

38* Implementation of the UK Newborn Screening Programme

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CF newborn screening (NBS) in the UK was developed to complement the national programme with IRT measurement on the day 5 blood spot sample. A cut-off of 99.5% would determine which samples were sent for DNA analysis for the 4 commonest UK mutations (one mutation would prompt analysis with a 29 mutation panel). A second IRT (IRT-2) would be measured in the third week of life in infants with one mutation (assessment including sweat test only if IRT-2 elevated). Second IRT measurements were also undertaken on infants with a very high initial IRT (>99.9th centile) and no mutation identified.

From April 2007 to March 2008, 589,931 infants were screened and 3253 referred for DNA analysis (0.55%). 149 babies had 2 CF mutations (in 40 the second mutation was recognised from the extended 29 mutation panel). A further 75 infants were referred for assessment following a raised IRT-2, 40 of whom had one mutation detected (complete data not yet available). 140 (0.023%) putative carriers were recognized (one mutation and IRT-2 not raised).

The UK programme has achieved its aim of limiting the number of families referred for assessment (sweat testing). This does not appear to be at the expense of case recognition. A positive aspect has been the low proportion of putative carriers; the reasons for this are less clear but may relate to IRT cut-offs and the limited panel of four mutations in the first DNA screen.

39 Proficiency Testing for CF Newborn Screening

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Objective: To serve the NBS community in the US and abroad, the Newborn Screening Quality Assurance Program developed 3 proficiency testing (PT) programs: immunoreactive trypsinogen (IRT), IRT/F508del, and multiple mutation detection.

Methods: Dried blood spot (DBS) materials for IRT testing were created using a whole blood matrix and IRT (2002-present). DBS materials for DNA testing were created using a whole blood matrix, IRT, and transformed lymphoblast cell lines containing 1 or 2 copies of the F508del mutation (2004–2008) or prepared from adult or adolescent CF patients (2007–2008). PT specimens were sent quarterly. Data collected included method used, clinical assessment, IRT concentration and/or genotype detected. Data was graded based on the clinical assessment.

Results: IRT and F508del data results are based on results from 2002–2007. The false negative rate for US and Canadian laboratories was 0.67% (n=1670 results) and 0.67% for foreign laboratories. 2% of DNA results were incorrect for US and Canadian laboratories (n=316 results) with a 1% sample failure rate and 7% of results were incorrect for foreign laboratories (n=3414 results) with a 10% sample failure rate. For the multiple mutation detection program, 8% of results from US and Canadian laboratories were not evaluated because of sample failure or because mutations could not be tested. Only 2% of results were incorrect (n=609 results). In contrast, 38% of results from foreign laboratories were not evaluated because of sample failure or because mutations could not be tested. Of the results evaluated, 6% were incorrect (n=295 results).

Conclusions: PT programs are an important component of monitoring laboratory performance. Overall, this data has shown that NBS laboratories worldwide are able to provide consistent, reliable results for CF NSB.

40 Survival analysis of CF patients diagnosed in a 35-year neonatal screening program in North-eastern Italy

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Between 1973 and 2008 426 patients (218F, 208M) have been diagnosed by the neonatal screening program in Veneto, a north-eastern region of Italy of approx 5 million inhabitants. We performed a survival analysis (Kaplan-Meier) and studied the influence on survival of relevant risk factors in pts diagnosed by symptoms. Similarly to the rest of Italian CF population, 80% of the CFTR mutations were accounted for by 8 mutation (F508del, R1162X, 2183AA → G, N1303K, G542X, 711+5G → A, 1717–1G → A, R553X). The n of deaths was 31 (14M, 17F). Survival probability exceeded 80% at 25 years. There was no significant difference in survival probability in M vs F, PI vs PS patients, diabetics vs non diabetics (defined by insulin treatment) although F tended to need insulin Tx earlier (log-rank test p=0.06) and tended to be listed earlier for lung transplant (p=0.07). We conclude that pts. diagnosed by neonatal screening have elevated survival probability through adulthood and survival is not affected by established risk factors in pts diagnosed by symptoms.

41 Towards a consensus on the early management of infants identified with cystic fibrosis following newborn screening (NBS)

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Introduction: The aim of this project was to determine a consensus with respect to the early management of infants recognised to have CF following NBS.

Methods: A modified Delphi methodology was used. A core group reviewed the literature, graded the available evidence and produced 41 statements. All members of the ECFS were invited to participate in the consensus via e mail. Additional invitations were made to increase multidisciplinary input. The specialist was asked to rate their agreement for each statement. In the case of disagreement, comments were requested. The level of agreement constituting consensus was determined a priori to be 80%. After round 1, statements not achieving consensus were modified by the core group, taking into account comments. In round two, the initial statements, degree of agreement, summary of comments, and a second set of proposed statements were circulated to all respondents. 4 additional statements were included based on participants' suggestions. The process is ongoing in order to achieve consensus for all statements.

Results: After two rounds of the Delphi process, 43 statements have >80% agreement and will go forward to the consensus document. In two statements consensus was not achieved. One statement considered whether and what blood tests were needed for a baseline assessment and the second was a new statement following suggestions from round 1, which discussed need for the family to contact the CF team at any time. The core group is currently reviewing these statements.

Conclusion: This methodology has enabled development of a consensus document that will provide a valuable tool for CF teams both with established programmes and those in the process of implementing NBS.